

BEST AVAILABLE COPY

(12) UK Patent Application (19) GB (11) 2 045 083 A

- (21) Application No 8005179
(22) Date of filing 15 Feb 1980
(30) Priority data
(31) 7902035
(32) 7 Mar 1979
(33) Sweden (SE)
(43) Application published
29 Oct 1980
(51) INT CL³
A61F 1/00
(52) Domestic classification
A5R AP
(56) Documents cited
GB 1530624
GB 1505215
GB 1463948
GB 1461420
GB 1416267
GB 1390445
GB 1319641
GB 1243375
(58) Field of search
A5R
(71) Applicants
Per Ingvar Branemark,
Andergatan 3,
S-431 39 Molndal,
Sweden.
Bo Thuresson Af
Ekenstam,
Vadmansgatan 16³,
S-412 53 Goteborg,
Sweden.
(72) Inventors
Per Ingvar Branemark,
Bo Thuresson Af
Ekenstam.
(74) Agents
J.A. Kemp & Co.

(54) Element for implantation in body tissue, particularly bone tissue

(57) An element for implantation in body tissue, particularly bone tissue, consists of a biologically flawless material with a micro-pitted surface. The pore diameter may be as little as 10 nm and as large as a few multiples of the normal diameter of the cells in the tissue, preferably no larger than the cell diameter, i.e. about 1000 nm. Optimal results are obtained with pore diameters equal to or smaller than about 300 nm and a finely pored rutile surface has been found to give a particularly strong and durable joint with the growing tissue. At least one deposit of an agent facilitating and/or accelerating the growing-together process is arranged on or in the element. The element may be shaped with grooves, corrugations or recesses and be provided with an opening for tissue to grow through. The element is extremely suitable as anchoring device for a prosthesis.

GB 2 045 083 A

SPECIFICATION

Element for implantation in body tissue, particularly bone tissue

- 5 The present invention relates to an element for implantation in body tissue, particularly bone tissue, in which the surface intended to face the body tissue is micro-pitted and the material of the element is
 10 selected to avoid the occurrence of unsuitable electrical potential differences and galvanic currents in the implantation region.

It is already known that with advances in surgical technique, and by suitable design of artificial implants, it is possible to achieve a more complete and permanent integration of an implant with the surrounding tissue.

It is of vital importance that improvements can be made to give a high frequency of successful operations with re-established biological function so that a second operation with the related traumatic consequences, both physiological and psychological, can be avoided, thus also relieving unnecessary strain on the medical resources.

- 25 Swedish Patent application No. 77 10 777-9 emphasizes the importance of having the carrier elements or implants described therein so designed as to achieve rapid re-establishment of the blood circulation around and through the carrier means.
 30 This requires considerably increased supply of biological media with a reconstructive effect. This reduces the time for healing, due to increased cell formation and more rapid mineralization of in-growing tissue. A considerably improved clinical result and shortened hospitalization time are then achieved.

For this desired result, it is of vital importance that the prosthesis or connecting material is formed as an integratable part of the bio-physiological milieu and that this material is in a biologically, physically 40 and biochemically optimal ratio to the bone tissue, which for the most part consists of Ca^{2+} , PO_4^{3-} and CO_3^{2-} ions with traces of other ionized substances occurring naturally in plasma or bone apatite.

Several research workers have stated that acceptable implantation has been obtained with a method, as described for example by Wheeler et al in Biomet., Med. Dev. Art. Org., 1(2), 337-348 (1973) and by Karagianes in Biomet., Med. Dev. Art. Org., 1(1), 171-181 (1973). The experiments recorded 50 include a couple of years' experience with apes. However, the result of experiments on animals should be interpreted with the utmost caution since there are vast differences between the physical-biophysiological situation of *homo* and of other species, even within the primate group.

According to one interpretation of Wheeler et al and Karagianes, their good results are due to the use of titanium alloyed cylindrical fixtures produced in various ways with a pore size varying within the 60 range 275-650 μm . The theory of the method entails having the implanted cylinders larger in diameter than the cylindrical cavities drilled for them in the bone of laboratory animal jaw bones and inserting them by applying mechanical pressure.

65 However, the implantation of such carrier ele-

ments does not appear to give optimal and permanent ingrowth.

The object of the present invention is to effect a carrier element with improved properties as regards 70 acceptance of the carrier element, primarily improved durability of the healthy ingrowth of the element due to its biological quality.

Accordingly the present invention provides an element intended for implantation in body tissue, 75 consisting of a biologically flawless material with a porous, micro-pitted surface intended to face the tissue in the implantation region of a patient, said material being selected to avoid the occurrence of unsuitable electrical potential differences and galvanic currents in the implantation region, wherein on or in the element is arranged at least one depot of at least one agent facilitating and/or accelerating the healing process of the body tissue on the element, wherein said agent contains enriched whole blood 80 or plasma from the patient into whom the element is or to be implanted by surgery.

An analysis of jaw implants *in homo* has unexpectedly shown that the operation results obtained are noticeably improved if the size of the micro-pitting approaches the order of magnitude of the cell diameter in the surrounding tissue or of a few multiples thereof. The normal cell size applicable is of the order of 1000nm (where 1 nm = 10 \AA). The bio-optimal result is achieved, however, if the pit 95 diameter is selected within the range 10 to 300 nm, which is considerably smaller than the cell diameter. Material which can be used for prostheses and connecting devices should therefore have a micro-pitted surface. The surface between living, ingrow-

100 ing cells and shoots to the cells in the mineralisation process shall, together with channelised material and laminae with collagen fibrils, form such a tight and extensive boundary limit to the connecting devices that these achieve reinforced and inextricable anchoring in the living bone tissue. In this way detachment of the implant from the boundary zone will be impossible. In experiments it has been found that fracturing occurs away from established boundary zones.

110 The material for the connecting device should thus preferably have a surface structure in which the diameter of the pits should be 10 to 1000 nm, where the upper limit of 1000 nm corresponds to the cell diameter, or more preferably 10 to 300 nm where the 115 upper limit of 300 nm corresponds to a transverse dimension of an offshoot from the tissue cell and of a fibril from bone tissue.

The mineralized constituents of the bone tissue are primarily hydroxyapatite having a composition 120 $\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2$. This general formula for a minimum harmonic molecule unit corresponds to a unit length of about 5 to 20 nm. The mineralized parts of the bone tissue also include a certain amount of Mg^{2+} , Na^+ and K^+ as well as CO_3^{2-} , Cl^- , F^- and citric acid. From the mineralogical point of view this confirms good experience in operating in implants having a pit diameter of 10 to 300 nm.

The P atoms in PO_4^{3-} are tetrahedrally interspersed and form a three dimensional, deformed 130 network in which the PO_4^{3-} ions are to a great extent

connected by hydrogen bonds to the surrounding material of mineralized and living tissue consisting of proteins and other membrane substances such as carbohydrates, or fatty substances.

5 The upper limit (of the same order of magnitude as the cell diameter) and the lower, even more optimal, pit diameter limit correspond to the dimensions of the cell shoots and bone tissue fibrils with the mineral components as above.

10 The formation of new bone tissue takes place from the surface of the bone tissue through the living cell system with the intra-cellular matrix consisting of collagen fibres and inorganic components.

The inorganic components in the resulting bone 15 constitute 2/3 of its weight. Of this 85% comprises calcium phosphate and about 10% comprises calcium carbonate. The collagen fibres contribute greatly to the strength and elasticity of the bone tissue. All bone cells are of the same basic type, 20 which undergo alterations at the same rate as the mineralization from osteoblasts via osteocytes to osteoclasts. Osteoclasts vary in appearance from cuboid to pyramid shapes oriented in continuous layers. The cytoplasma is characterised by the

25 presence of ribonucleo protein which synthesizes protein components for the bone matrix. The osteoblasts contain the enzyme alkaline phosphatase which not only develops the matrix but is also responsible for the mineralization process. The 30 osteoblasts are thereby transformed to osteocytes, fully developed bone cells, within the frame of the bone matrix. The cytoplasma of the osteoblasts contains fat, a certain amount of glycogen and fine granules. Direct contact between adjacent osteob-

35 lasts occurs during the bone building process. The process conserves a highly developed channel system for the exchange of metabolites between the bone cells and the vessel bed (the blood circulation).

The osteoclasts are a bone cell type, with wide 40 variation in size, which can be found in the bone surface and consist of what are known as fused cells, giant cells having several cores. The surrounding bone tissue often appears to be partially demineralized and it is therefore assumed that this type of cell 45 is a phase in the resorption of bone during the rebuilding phase.

In the bone matrix, the osteocollagen fibres are held together by a cement substance consisting substantially of mucopoly saccharides (chondroitin 50 sulphate). The mineral substances of the bone are exclusively localized to the cement between the fibres and consist essentially of crystals of calcium phosphate of the hydroxy apatite type of crystal in the form of high density particles arranged perpendicularly to the osteocollagen fibres. The bone matrix is arranged in laminated form, the laminae having a thickness of 3 to 7 μ m. The collagen fibres have transverse corrugation at a recurrent distance of 68 nm between the fibres. This confirms the correctness of the technical implementation of the material substitute to be selected as carrier element or replacement for traumatized tissue.

The mechanical or metallurgical production methods used should be such that both the number 65 of micro-pits and the pit diameter in the material

used gives it even greater total ingrowth surface between implant and newly formed tissue. It has also been found advantageous to provide the implant with large through openings for bone tissue to

70 grow through.

Furthermore, the connecting devices shall be manufactured from biologically flawless material which cannot give rise to unsuitable differences in electrical potential or galvanic currents in the implant regions. Special materials such as titanium, titanium alloys, ceramic material or metal covered with ceramic material have been found to give acceptable biological integration.

Of the various materials which may be selected as 80 starting material for optimally integratable connecting devices, titanium is, due to its proximity to Ca in the periodic table and its chemical inertness, supposed to be an extremely suitable basic material both as attachment device and prosthesis and also 85 as replacement for soft tissue. Experiments have shown that no titanium has migrated into the surrounding tissue from unalloyed titanium implanted into various types of tissue by surgery.

The titanium material to be used for osteointegration 90 should preferably be totally unalloyed, at least in the boundary zone between living tissue and implanted titanium.

The importance of the surface structure of the titanium material has been emphasized above, and 95 in the case of titanium the surface structure is effected by scoring the surface with a cutting rate of less than 20 m/min under air or other oxygen gas cooling, such as O₂ or stabilized hydrogen superoxide. The cutting speed is kept low to give the process 100 sufficient time to provide oxidization of the work-piece. The oxidization entails the formation of titanium oxides which, due to their mineralogical properties, promote the formation of a biologically appropriate surface structure of micro-pitted type 105 (moon surface type).

Of course the surface may be produced in some other manner, such as by sintering or metal vaporization in inert gas. However, the most economic method appears to be preparation with a cutting tool. The surface may also be ceramicized only with 110 other biological, negatively charged ions such as phosphates (phosphatizing), phosphates + O₂, and other combinations with small quantities of sulphate, fluoride, chloride and a certain basic carbonization.

When stored, titanium (and even low-alloyed titanium after machining) quickly acquires an oxidized surface equivalent to a crystallized surface of rutile, TiO₂, whereupon the oxygen content of the 120 titanium drops from the surface layer inwards until the oxygen content reaches a value of 0.

The deformed bone apatite tends to form strong bonds over its monocline and tetrahedrally (hexagonally) faceted structure with the finely pored 125 rutile deposit of the titanium material, since the cubic molecule lattices of the rutile and the hexagonal molecule lattices of the bone apatite fit excellently together.

It is of the greatest importance that the healing 130 process is given optimal opportunity with respect to

(a) the substrate supplied, (b) enzyme activity and (c) mineralization.

This is achieved by providing the carrier element or connecting device, as well as the prosthesis material, with suitably located resorbable depots in ridges, punched recesses or applied surface layer. A combination of these alternatives may, of course, also be used. Between the fibres known as tropocollagen fibres, which can be seen as monomolecular conglomerate, there is a gap of 40 nm from the end of one fibre to the beginning of the next. The total collagen conglomerate consists of three collagen threads, each comprising a triple helix of osteotrope collagen fibres.

15 Dominant amino acids in the peptide chains of the collagen which are difficult to dissolve are glycine, about 30%, and proline. Such a peptide chain contains proline frequently peptidized with glycine. The proline is hydroxylated into a 4-stand by pro-
20 tocollagen-hydroxylase. Vitamin C is required to accelerate the process. By means of a corresponding mechanism some of the lower lysis content of the collagen is transformed to hydroxylysine. The hydroxy group of this amino acid is connected in a
25 covalent bond with disaccharides consisting of galactose and glucose. The "fibre gap" described forms the centre for the mineralization of the bone tissue.

Experimental experience establishes the necessity 30 of such a micro-pitted surface on the bone substitute material that in its network of pits the pit diameter is so small that it can form three dimensional deposit points for (a) end terminal collagen fibre groups, (b) carbohydrate groups of the collagen and (c) collagen 35 fibres with bone mineral while at the same time forming covalent bonds and inter-molecular binding forces in a network and space pattern which is as close as possible (5 to 500 nm). The prerequisites for a durable bond between living tissue and a substi-
40 tute for living tissue are based on the relevant knowledge gathered about the collagen fibre system of the various types of tissue with interspersed minerals which have been specialized to the biological function of each tissue.

45 It is clear from the above which biological requirements must be met with respect to the aim of establishing a boundary zone, between living tissue and an implant, which is as firmly anchored as possible.

50 Over many years of experimental work firm joints have been achieved with materials prepared in various manners, the surfaces of the connecting device being shaped with increased surface contact by means of corrugation and threading thereof.

55 By carefully screw-threading the fixture material a healthy and strong bone surface is obtained with exact anatomical sealing congruence to the implant surface, thus giving a controlled compression of the bone tissue. Experience has shown that careful
60 threading of drill-holes in the bone tissue and of the corresponding implant using cutting tools of titanium working at low speed gives the best seal and a greatly optimized and increased adhesion and healing surface between the implant and the living tissue
65 prepared for operation, without producing any cuts

in the tissue, for example due to metal particles which might be caused by other faster-working tools.

Swedish Patent No. 77 10 777-9 describes an 70 embodiment of the prosthesis and connecting devices permitting the application of depots either in or on them. Agents such as membrane effects, mineral substances, blood vessel dilator, coagulation-regulator, vitamins and growth-promoting hormones 75 are incorporated in these depots. The agent may be applied to the material surfaces, or arranged in the form of suitably arranged depots consisting of fully resorbable material innocuous to the tissue. Another variant which has now been found by experiment to 80 be able to improve the healing result is treating the material intended for operation by means of dipping, or some other form of surface contact, with whole blood or plasma possibly enriched before the operation with desired nutritional and therapeutic agents 85 including desirable proenzymes, enzymes, hormones, specific substrates and vitamins.

The utilization of the principles described above for producing a carrier element according to the invention gives greatly improved results if the 90 material having the required purity, shape, and surface structure (the latter determined in a scanning transmission electron microscope) is combined with depots of nutrients or is treated with enriched whole blood or plasma. It should be observed in this case 95 that the patients' blood group and plasma quality have been adequately tested. Enriched blood or plasma from the patient himself is most advantageous to use.

The requirements specified, including the pore 100 size, are applicable to all material selected for biological integration, for attachment devices for prostheses for use in the cranial bones, joints, soft tissue or soft tissue transition.

By implanting prosthetic appliances in the healing 105 process to repair all types of tissue defects, regardless of whether these are the result of pathological processes or of traumatic influences, it is expected that all such healing processes will be strongly dependent upon biochemical reactions which guide 110 the balancing of the control of the coagulation factors, the regrowth of the capillary bed, the addition of vital nourishing substances, and the provision of an adequate immunity. In the said Swedish Patent Application No. 7710777-9, the 115 considerable importance of the prosthetic material has been stressed, and so have the healing properties of the living tissues. Thus, it has been strongly emphasised that the design and choice of all prosthetic material should be chosen carefully, with rigid 120 requirements of the material which should constantly and functionally be accepted by the living tissue, whether soft or boney. Administration of growth-promoting substances may be general or local. In the case of local administration, four possible means 125 of distribution are acceptable; these are:-
1. Administration of growth-promoting substances orally by enrichment of the nutrition, both pre- and post-operatively.
2. In some cases administration of growth-promoting substances by parenteral methods, both

pre-and post-operatively.

3. The operative area can be treated locally by enrichment of the patient's own plasma or blood, or pre-analysed plasma may be considered adequate.

5 4. The prosthetic material may be treated before use with enriched plasma or whole blood. Irrespective of the nature of the prosthetic material, it should be given such a surface structure as to ensure an increased deposition of enriched plasma or whole 10 blood.

The structure of the prosthetic material should enable such a quantitative deposition of biologically optimal growth factors, in order that these may be brought into the reconstructive area during the most 15 intensive growth phase. Functional depots are formed in the prosthetic material in such a way that they may be used pre- or intra-operatively. The depots are manufactured of such materials which have been found to be immunologically acceptable 20 and bio-degradable.

Thus either a biological material from treated patients, or certain selected plastics materials, may be used. Especially, bone, cartilage or collagen tissue from treated patients can be considered. The 25 materials are preferably freeze-dried, whereafter enriched plasma or whole blood is added. Surplus material is removed and the above-mentioned depot can immediately be used, or may undergo a renewed freeze-drying procedure for later use. The 30 depot areas in the prosthetic material are chosen in such a way that they are brought into intimate and adequate contact with tissue adjacent to the prosthesis.

Biologically important substances for general or 35 local treatment or administration, include:-
 (a) amino acids, especially proline and glycine;
 (b) blood factors balancing the coagulation ability;

(c) substances which positively affect the circulatory bed volume and oxygenation;

(d) vitamins, especially ascorbic acid and nicotinic acid compounds, whereby ascorbic acid is mandatory for a normal collagenisation;

(e) phosphate, primarily in the form of calcium 45 phosphate with supplements by other materials such as sodium, potassium, magnesium, zinc, etc. (the phosphate ought to be completed by lesser amounts of chloride and fluoride ions);

(f) mesoinosite (an important substance which 50 should be included);

(g) growth hormones are especially added to local depots or as finish on the prosthetic material, whereby fibrine is used as a covering layer;

(h) as protection against infection, broad- 55 spectrum antibiotics are used and may be locally administered in the above described manner;

(i) enrichment by the depot principle, using leukocytes in excess and/or interferone.

The list of growth-biochemicals can naturally be 60 added to, using the described method.

The above described technique can be further developed by compensating the need for substances promoting biological growth, using separate packages, or using pre-manufactured depots of different 65 size, which may be stored before use in connection

with reconstructive surgery. The packages containing sterile products should be hermetically sealed, to be opened just before the operation, or intraoperatively.

70

CLAIMS

1. An element intended for implantation in body tissue, consisting of a biologically flawless material 75 with a porous, micro-pitted surface intended to face the tissue in the implantation region of a patient, said material being selected to avoid the occurrence of unsuitable electrical potential differences and galvanic currents in the implantation region, where- 80 in on or in the element is arranged at least one depot of at least one agent facilitating and/or accelerating the healing process of the body tissue on the element, wherein said agent contains enriched whole blood or plasma from the patient into whom 85 the element is to be implanted by surgery.

2. An element according to claim 1, wherein said agent is selected from a group consisting of substances having membrane effects, mineral substances, blood vessel-dilating substances, coagula- 90 tion-regulating substances, vitamins and growth-promoting hormones.

3. An element according to claim 1 or 2, wherein the pores in the porous surface have a diameter in the range of from about 10 nm up to at most a few 95 multiples of the normal cell diameter of body tissue.

4. An element according to claim 1, 2 or 3, wherein the upper limit of the range of pit diameters is about 1000 nm.

5. An element according to claim 1, 2 or 3, 100 wherein the upper limit of the range of pit diameters is about 300 nm.

6. An element according to any one of claims 1 to 5, wherein the porous surface at least substantially consists of a fine-pored rutile layer.

105 7. An element according to any one of claims 1 to 6, wherein the porous surface has grooves, corruga- tions, channels and similar recesses roughening the surface.

8. An element according to any one of claims 1 to 110 7, wherein at least one through opening is provided for tissue to grow through, said opening arranged in the element and being many times greater than the pore diameter.

9. An element according to any one of the 115 preceding claims wherein said at least one depot includes amino acids.

10. An element according to any one of the preceding claims wherein said at least one depot includes blood factors balancing the coagulation 120 ability.

11. An element according to any one of the preceding claims wherein said at least one depot includes substances which benefit the circulatory bed volume and oxygenation.

125 12. An element according to any one of the preceding claims wherein said at least one depot includes vitamins.

13. An element according to any one of the preceding claims wherein said at least one depot 130 includes a phosphate.

14. An element according to any one of the preceding claims wherein said at least one depot includes a growth hormone.
15. An element according to any one of the preceding claims wherein said at least one depot includes a broad-spectrum antibiotic.
16. An element according to any one of the preceding claims wherein said at least one depot includes leukocytes in excess and/or interferone.
- 10 17. An element intended for implantation in body tissue, such element being according to claim 1 and substantially as hereinbefore described.

Printed for Her Majesty's Stationery Office by Croydon Printing Company Limited, Croydon, Surrey, 1980.
Published by the Patent Office, 25 Southampton Buildings, London, WC2A 1AY,
from which copies may be obtained.



05
P.M.J. (D)

(12) UK Patent (19) GB (11) 2 045 083 B

SCIENCE REFERENCE LIBRARY

(54) Title of invention

Element for implantation in body tissue
particularly bone tissue

(51) INT CL³; A61F 1/00

(21) Application No
8005179

(22) Date of filing
15 Feb 1980

(30) Priority data

(31) 7902035

(32) 7 Mar 1979

(33) Sweden (SE)

(43) Application published
29 Oct 1980

(45) Patent published
11 Jan 1984

(73) Proprietors
Per Ingvar Branemark
Andergatan 3
S-431 39 Molndal
Sweden
Bo Thuresson Af Ekenstam
Vadmansgatan 163
S-412 53 Goteborg
Sweden

(72) Inventors
Per Ingvar Branemark
Bo Thuresson Af Ekenstam

(52) Domestic classification
A5R AP AG

(56) Documents cited
GB 1602932
GB 1552388
GB 1530624
GB 1505215
GB 1463948
GB 1461420
GB 1416267
GB 1390445
GB 1319641
GB 1243375
GB 990126

(74) Agent and/or
Address for Service
J. A. Kemp and Co.,
14 South Square,
Gray's Inn,
London WC1R 5EU

(58) Field of search
A5R

-1-

DESCRIPTION

"ELEMENT FOR IMPLANTATION IN BODY
TISSUE, PARTICULARLY BONE TISSUE"

The present invention relates to an element for implantation in body tissue, particularly bone tissue, in which the surface intended to face the body tissue is micro-pitted and the material of the element 5 is selected to avoid the occurrence of unsuitable electrical potential differences and galvanic currents in the implantation region.

It is already known that with advances in surgical technique, and by suitable design of artificial 10 implants, it is possible to achieve a more complete and permanent integration of an implant with the surrounding tissue.

It is of vital importance that improvements can be made to give a high frequency of successful 15 operations with re-established biological function so that a second operation with the related traumatic consequences, both physiological and psychological, can can be avoided, thus also relieving unnecessary strain on the medical resources.

20 Swedish Patent application No. 77 10 777-9 emphasizes the importance of having the implantation elements described therein so designed as to achieve

rapid re-establishment of the blood circulation around and through the element. This requires considerably increased supply of biological media with a reconstructive effect. This reduces the time for 5 healing, due to increased cell formation and more rapid mineralization of in-growing tissue. A considerably improved clinical result and shortened hospitalization time are then achieved.

For this desired result, it is of vital 10 importance that the prosthesis or mounting element is formed as an integratable part of the bio-physiological milieu and that this material is in a biologically, physically and biochemically optimal ratio to the bone tissue, which for the most part consists of Ca^{2+} , PO_4^{3-} and CO_3^{2-} ions with traces of other ionized substances 15 occurring naturally in plasma or bone apatite.

Several research workers have stated that acceptable implantation has been obtained with a method, as described for example by Wheeler et al in Biomet., 20 Med. Dev. Art. Org., 1(2), 337-348 (1973) and by Karagianes in Biomet., Med. Dev. Art. Org., 1(1), 171-181 (1973). The experiments recorded include a couple of years' experience with apes. However, the result of experiments on animals should be interpreted with the 25 utmost caution since there are vast differences between the physical-biophysiological situation of homo and of

other species, even within the primate group.

According to one interpretation of Wheeler et al and Karagianes, their good results are due to the use of titanium alloyed cylindrical fixtures produced

- 5 in various ways with a pore size varying within the range 275-650 μm . The theory of the method entails having the implanted cylinders larger in diameter than the cylindrical cavities drilled for them in the bone of laboratory animal jaw bones and inserting them by applying
- 10 mechanical pressure.

However, the use of such implantation elements does not appear to give optimal and permanent ingrowth.

- The object of the present invention is to effect an implantation element with improved properties as regards
- 15 acceptance of the implantation element, primarily improved durability of the healthy ingrowth of the element due to its biological quality.

- Accordingly the present invention provides an element intended for implantation in body tissue,
- 20 consisting of a biologically flawless material selected to avoid the occurrence of unsuitable electrical potential differences and galvanic currents in the implantation region, said element having as the surface intended to face the tissue in the implantation region of a patient a porous
 - 25 surface which is additionally micro-pitted the pits having a diameter in the range of from substantially 10 nm to

substantially 1000nm.

An analysis of jaw implants in homo has unexpectedly shown that the operation results obtained are noticeably improved if the size of the micro-pitting is as small as the order of magnitude of the cell diameter in the surrounding tissue or at most of a few multiples thereof. The normal cell size applicable is of the order of 1000nm (where 1 nm = 10⁹ Å). The bio-optimal result is achieved, however, if the pit diameter is selected within the range 10 to 300 nm, which is considerably smaller than the cell diameter. Material which can be used for prostheses and mounting elements should therefore have a micro-pitted surface. The surface between living, ingrowing cells and shoots to the cells in the mineralisation process shall, together with channelised material and laminae with collagen fibrils, form such a tight and extensive boundary limit to the mounting elements that these achieve reinforced and inextricable anchoring in the living bone tissue. In this way detachment of the implantation element from the boundary zone will be impossible. In experiments it has been found that fracturing occurs away from

established boundary zones.

The material for the implantation element should thus have a surface structure in which the diameter of the pits should be 10 to

5 1000 nm, where the upper limit of 1000 nm corresponds to the cell diameter, or more preferably 10 to 300 nm where the upper limit of 300 nm corresponds to a transverse dimension of an offshoot from the tissue cell and of a fibril from bone tissue.

10 The mineralized constituents of the bone tissue are primarily hydroxy apatite having a composition $\text{Ca}_{10} (\text{PO}_4)_6(\text{OH})_2$. This general formula for a minimum harmonic molecule unit corresponds to a unit length of about 5 to 20 nm. The mineralized parts 15 of the bone tissue also include a certain amount of Mg^{2+} , Na^+ and K^+ as well as CO_3^{2-} , Cl^- , F^- and citric acid. From the mineralogical point of view this confirms good experience in operating in implants having a pit diameter of 10 to 300 nm.

20 The P atoms in PO_4^{3-} are tetrahedrally interspersed and form a three dimensional, deformed network in which the PO_4^{3-} ions are to a great extent connected by hydrogen bonds to the surrounding material of mineralized and living tissue consisting 25 of proteins and other membrane substances such as carbohydrates, or fatty substances.

The upper limit (of the same order of magnitude as the cell diameter) and the lower, even more optimal, pit diameter limit correspond to the dimensions of the cell shoots and bone tissue fibrils with the mineral components as above.

5

The formation of new bone tissue takes place from the surface of the bone tissue through the living cell system with the intra-cellular matrix consisting of collagen fibres and inorganic components.

10

The inorganic components in the resulting bone constitute 2/3 of its weight. Of this 85% comprises calcium phosphate and about 10% comprises calcium carbonate. The collagen fibres contribute greatly to the strength and elasticity of the bone tissue. All bone cells are of the same basic type, which undergo alterations at the same rate as the mineralization from osteoblasts via osteocytes to osteoclasts. Osteoclasts vary in appearance from cuboid to pyramid shapes oriented in continuous layers.

15

The cytoplasma is characterised by the presence of ribonucleo protein which synthesizes protein components for the bone matrix. The osteoblasts contain the enzyme alkaline phosphatase which not only develops the matrix but is also responsible for the mineralization process. The osteoblasts are thereby transformed to osteocytes, fully developed bone

25

cells, within the frame of the bone matrix.

The cytoplasma of the osteoblasts contains fat, a certain amount of glycogen and fine granules.

5 Direct contact between adjacent osteoblasts occurs during the bone building process. The process conserves a highly developed channel system for the exchange of metabolites between the bone cells and the vessel bed (the blood circulation).

10 The osteoclasts are a bone cell type, with wide variation in size, which can be found in the bone surface and consist of what are known as fused cells, giant cells having several cores. The surrounding bone tissue often appears to be partially demineralized and it is therefore assumed that this
15 15 type of cell is a phase in the resorption of bone during the rebuilding phase.

20 In the bone matrix, the osteocollagen fibres are held together by a cement substance consisting substantially of mucopoly saccharides (chondroitin sulphate). The mineral substances of the bone are exclusively localized to the cement between the fibres and consist essentially of crystals of calcium phosphate of the hydroxy apatite type of crystal in the form of high density particles arranged perpendicularly
25 to the osteocollagen fibres. The bone matrix is arranged in laminated form, the laminae having a

thickness of 3 to 7 μm . The collagen fibres have transverse corrugation at a recurrent distance of 68 nm between the fibres. This confirms the correctness of the technical implementation of the material substitute to be selected as implantation element for traumatized tissue.

The mechanical or metallurgical production methods used should be such that both the number of micro-pits and the pit diameter in the material used gives it even greater total ingrowth surface between implant and newly formed tissue. It has also been found advantageous to provide the implant with at least one through opening for bone tissue to grow through, the or each such opening being many times greater than the pit diameter.

Furthermore, the biologically flawless material used for the implantation elements in accordance with the present invention may comprise special materials such as titanium, titanium alloys, ceramic material or metal covered with ceramic material. These have been found to give acceptable biological integration.

Of the various materials which may be selected as starting material for optimally integratable implantation elements, titanium is, due to its proximity to Ca in the periodic table and its chemical inertness, supposed to be an extremely suitable basic material both

be used. Between the fibres known as tropacollagen fibres, which can be seen as monomolecular conglomerate, there is a gap of 40 nm from the end of one fibre to the beginning of the next. The total collagen

5 conglomerate consists of three collagen threads, each comprising a triple helix of osteotrope collagen fibres.

Dominant amino acids in the peptide chains of the collagen which are difficult to dissolve are glycine, about 30%, and proline. Such a peptide chain

10 contains proline frequently peptidized with glycine. The proline is hydroxylated into a 4-stand by protocollagen-hydroxylase. Vitamin C is required to accelerate the process. By means of a corresponding mechanism some of the lower lysis content of the collagen

15 is transformed to hydroxylysine. The hydroxy group of this amino acid is connected in a covalent bond with disaccharides consisting of galactose and glycose. The "fibre gap" described forms the centre for the mineralization of the bone tissue.

20 Experimental experience establishes the necessity of such a micro-pitted surface on the bone substitute material that in its network of pits the pit diameter is so small that it can form three dimensional deposit points for (a) end terminal collagen

25 fibre groups, (b) carbohydrate groups of the collagen and (c) collagen fibres with bone mineral while at the

BEST AVAILABLE COPY

-9-

as mounting element and prosthesis and also as replacement for soft tissue. Experiments have shown that no titanium has migrated into the surrounding tissue from unalloyed titanium implanted into various
5 types of tissue by surgery.

The titanium material to be used for osteointegration should preferably be totally unalloyed, at least in the boundary zone between living tissue and implanted titanium.

10 The importance of the surface structure of the titanium material has been emphasized above, and in the case of titanium the surface structure is effected by scoring the surface with a cutting rate of less than 20 m/min under air or other oxygen gas cooling, such as
15 O₂ or stabilized hydrogen superoxide. The cutting speed is kept low to give the process sufficient time to provide oxidization of the workpiece. The oxidization entails the formation of titanium oxides which, due to their mineralogical properties, promote
20 the formation of a biologically appropriate surface structure of micro-pitted type (giving a "moon surface" appearance under microscopic examination).

Of course the micro-pitted surface may be produced in some other manner, such as by sintering or metal
25 vaporization in inert gas. However, the most economic method appears to be preparation with a cutting tool. The surface may also be ceramicized only with other

BEST AVAILABLE COPY

-12-

same time forming covalent bonds and inter-molecular binding forces in a network and space pattern which is as close as possible (5 to 500 nm). The prerequisites for a durable bond between living tissue and a substitute for living tissue are based on the relevant knowledge gathered about the collagen fibre system of the various types of tissue with interspersed minerals which have been specialized to the biological function of each tissue.

It is clear from the above which biological requirements must be met with respect to the aim of establishing a boundary zone, between living tissue and an implant, which is as firmly anchored as possible.

Over many years of experimental work firm joints have been achieved with materials prepared in various manners, the surfaces of the implantation element being shaped with increased surface contact by means of grooving, channelling, corrugation and screw threading thereof. By carefully screw-threading the implantation element a healthy and strong bone surface is obtained with exact anatomical sealing congruence to the implant surface, thus giving a controlled compression of the bone tissue. Experience has shown that careful threading of drill-holes in the bone tissue and of the corresponding implant using cutting tools of titanium working at low speed gives the best seal and a greatly

biological, negatively charged ions such as phosphates (phosphatizing), phosphates + O_2 , and other combinations with small quantities of sulphate, fluoride, chloride and a certain basic carbonization.

5 When stored, titanium (and even low-alloyed titanium after machining) quickly acquires an oxidized surface equivalent to a crystallized surface of rutile, TiO_2 , whereupon the oxygen content of the titanium drops from the surface layer inwards until
10 the oxygen content reaches a value of 0.

The deformed bone apatite tends to form strong bonds over its monocline and tetrahedrally (hexagonally) faceted structure with the finely pored rutile deposit of the titanium material, since the
15 cubic molecule lattices of the rutile and the hexagonal molecule lattices of the bone apatite fit excellently together.

It is of the greatest importance that the healing process is given optimal opportunity with respect
20 to (a) the substrate supplied, (b) enzyme activity and (c) mineralization.

This is achieved by providing the mounting implantation element, as well as the material of the prosthesis mounted thereby, with suitably located resorbable
25 depots in ridges, punched recesses or applied surface layer. A combination of these alternatives may, of course, also

optimized and increased adhesion and healing surface between the implantation element and the living tissue prepared for operation, without producing any cuts in the tissue, for example due to metal particles which might be 5 caused by other faster-working tools. According to the present invention such surface is furthermore micro-pitted.

Swedish Patent No. 77 10 777-9 describes an embodiment of the prosthesis and mounting implantation element permitting the application of depots either in or on 10 them. Such depots can be used with the element of the present invention. Agents such as membrane effects, mineral substances, blood vessel dilator, coagulation-regulator, vitamins and growth-promoting hormones are incorporated in these depots. The agent may be applied to 15 the material surfaces, or arranged in the form of suitably arranged depots consisting of fully resorbable material innocuous to the tissue. Another variant which has now been found by experiment to be able to improve the healing result is treating the material intended for 20 operation by means of dipping, or some other form of surface contact, with whole blood or plasma possibly enriched before the operation with desired nutritional and therapeutic agents including desirable proenzymes, enzymes, hormones, specific substrates and vitamins.

25 The utilization of the principle described above for producing an implantation element according to the invention gives greatly improved results if the material having the required purity, shape, and surface structure

(the latter determined in a scanning transmission electron microscope) is combined with depots of nutrients and/or is treated with enriched whole blood or plasma. It should be observed in this case that the 5 patients' blood group and plasma quality have been adequately tested. Enriched blood or plasma from the patient himself is most advantageous to use.

The requirements specified, including the pit size, are applicable to all material selected for 10 biological integration, for mounting implantation elements for prostheses for use in the cranial bones, joints, soft tissue or soft tissue transition.

By implanting prosthetic appliances in the healing process to repair all types of tissue defects, 15 regardless of whether these are the result of pathological processes or of traumatic influence, it is expected that all such healing processes will be strongly dependent upon biochemical reactions which guide the balancing of the control of the coagulation factors, the regrowth of 20 the capillary bed, the addition of vital nourishing substances, and the provision of an adequate immunity. In the said Swedish Patent Application No. 7710777-9, the considerable importance of the prosthetic material has been stressed, and so have the healing properties 25 of the living tissues. Thus, it has been strongly emphasised that the design and choice of all prosthetic

~~BEST AVAILABLE COPY~~

BEST AVAILABLE COPY

- 15 -

material should be chosen carefully, with rigid requirements of the material which should constantly and functionally be accepted by the living tissue, whether soft or boney. Administration of growth-

5 promoting substances may be general or local. In the case of local administration, four possible means of distribution are acceptable; these are:-

10 1. Administration of growth-promoting substances orally by enrichment of the nutrition, both pre- and post-operatively.

15 2. In some cases administration of growth-promoting substances by parenteral methods, both pre- and post-operatively.

3. The operative area can be treated locally by enrichment of the patient's own plasma or blood, or pre-analysed plasma may be considered adequate.

20 4. The prosthetic material may be treated before use with enriched plasma or whole blood. Irrespective of the nature of the prosthetic material, it should be given such a surface structure as to ensure an increased deposition of enriched plasma or whole blood.

The structure of the prosthetic material should enable such a quantitative deposition of biologically optimal growth factors, in order that these 25 may be brought into the reconstructive area during the most intensive growth phase. Functional depots are formed

BEST AVAILABLE COPY

- 16 -

in or on the prosthetic material of the implantation element in such a way that they may be used pre- or intra-operatively. The depots are manufactured of such materials which have been found to facilitate and/or accelerate 5 the healing process of the body tissue on the element and to be immunologically acceptable and bio-degradable.

Thus either a biological material from patients to be treated, or certain selected plastics materials, may be used. Especially, bone, cartilage or collagen tissue 10 from such patients can be considered. The materials are preferably freeze-dried, whereafter enriched plasma or whole blood is added. Surplus material is removed and the above-mentioned depot can immediately be used, or may undergo a renewed freeze-drying procedure for 15 later use. The depot areas in the prosthetic material are chosen in such a way that they are brought into intimate and adequate contact with tissues adjacent to the prosthesis.

Biologically important substances for general 20 or local treatment or administration, include:-

- (a) amino acids, especially proline and glycine;
- (b) blood factors balancing the coagulation ability;
- (c) substances which positively affect the circulatory bed volume and oxygenation;
- 25 (d) vitamins, especially ascorbic acid and nicotinic acid compounds, whereby ascorbic acid is mandatory for a normal collagenisation;
- (e) phosphate, primarily in the form of calcium

BEST AVAILABLE COPY

- 17 -

phosphate with supplements by other materials such as sodium, potassium, magnesium, zinc, etc. (the phosphate ought to be completed by lesser amounts of chloride and fluoride ions);

- (f) mesoinosite (an important substance which should be included);
5 (g) growth hormones are especially added to local depots or as finish on the prosthetic material, whereby fibrine is used as a covering layer;
10 (h) as protection against infection, broad-spectrum antibiotics are used and may be locally administered in the above described manner;
15 (i) enrichment by the depot principle, using leukocytes in excess and/or interferone.
The list of growth-biochemicals used in the described method can naturally be added to.

The above described technique can be further developed by adding the required substances promoting biological growth, using separate packages of such healing and facilitating or accelerating agents, or providing 20 various different pre-manufactured depots of different size of such substances, which depots may be stored before use in connection with reconstructive surgery. The packages containing sterile products should be hermetically sealed, to be opened just before the operation, or intraoperatively.

CLAIMS

1. An element intended for implantation in body tissue, consisting of a biologically flawless material selected to avoid the occurrence of unsuitable electrical potential differences and galvanic currents in the 5 implantation region, said element having as the surface intended to face the tissue in the implantation region of a patient a porous surface, which is additionally micro-pitted the pits having a diameter in the range of from substantially 10 nm to substantially 1000nm.
- 10 2. An element according to claim 1, wherein the upper limit of the range of pit diameters is substantially 300nm.
- 15 3. An element according to either of claims 1 and 2, wherein the porous micro-pitted surface substantially consists of a fine-pored rutile layer.
- 20 4. An element according to any one of claims 1 to 3, wherein the porous micro-pitted surface is a surface formed with grooves, corrugations, channels and similar recesses roughening the micro-pitted surface.
5. An element according to any one of claims 1 to 4, wherein at least one through opening is provided for tissue to grow through, said opening being arranged in the element and being many times greater than the pit diameter.

6. An element according to any one of claims 1 to 5, wherein said material is titanium having a decreasing oxygen content from a titanium dioxide micro-pitted surface inwardly.

5 7. An element according to any one of the preceding claims wherein on or in the element is arranged at least one depot of at least one agent facilitating and/or accelerating the healing process of the body tissue on the element.

10 8. An element according to claim 7, wherein a said depot includes whole blood or plasma taken from the patient into whom the element is to be implanted by surgery.

9. An element according to claim 7 or 8, 15 wherein a said depot includes a substance selected from a group consisting of substances having membrane effects, mineral substances, blood vessel-dilating substances, coagulation-regulating substances, vitamins and growth-promoting hormones.

20 10. An element according to claim 7, 8 or 9, wherein said at least one depot is within said element.

11. An element according to any one of claims 7 to 10, wherein a said depot includes an amino acid.

25 12. An element according to any one of claims 7 to 11, wherein a said depot includes a blood factor balancing the coagulation ability.

11 14-08-94

BEST AVAILABLE COPY

- 20 -

13. An element according to any one of claims 7 to 12, wherein a said depot includes a substance which benefits the volume and the degree of oxygenation of the blood circulation bed.

5 14. An element according to any one of claims 7 to 13, wherein a said depot includes a vitamin.

15. An element according to any one of claims 7 to 14, wherein a said depot includes a phosphate.

16. An element according to any one of claims 10 7 to 15, wherein a said depot includes a growth hormone.

17. An element according to any one of claims 7 to 16, wherein a said depot includes a broad-spectrum antibiotic.

18. An element according to any one of claims 15 7 to 17, wherein a said depot includes leukocytes in excess and/or interferone.

19. An element intended for implantation in body tissue, such element being according to claim 1 and substantially as hereinbefore described.

The text of the specification has been reproduced by photocopying the applicants original typescript. It may contain a few amendments which are difficult to read. The original typescript containing these amendments may be inspected on the premises of the Patent Office.

**This Page is Inserted by IFW Indexing and Scanning
Operations and is not part of the Official Record**

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

- BLACK BORDERS**
- IMAGE CUT OFF AT TOP, BOTTOM OR SIDES**
- FADED TEXT OR DRAWING**
- BLURRED OR ILLEGIBLE TEXT OR DRAWING**
- SKEWED/SLANTED IMAGES**
- COLOR OR BLACK AND WHITE PHOTOGRAPHS**
- GRAY SCALE DOCUMENTS**
- LINES OR MARKS ON ORIGINAL DOCUMENT**
- REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY**
- OTHER:** _____

IMAGES ARE BEST AVAILABLE COPY.

As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.